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09/620,783	07/21/2000	Howard Green	H0535/7012 /ERG/MAT	4731

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EXAMINER	
NAFF, DAVID M	
ART UNIT	PAPER NUMBER
1651	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Application No.	Applicant(s)
09/620783	Green et al

Examiner	Group Art Unit
Naff	1651

Office Action Summary

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 2/11/02.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-24, 51, 75-77, 102, 117-119, 123-125, 135, 136, 143+144 is/are pending in the application.

Of the above claim(s) ___ is/are withdrawn from consideration.

☐ Claim(s) ___ is/are allowed.

☒ Claim(s) 1-24, 51, 75-77, 102, 117-119, 123-125, 135, 136, 143+144 ~~1-3, 14, 23, 24, 34, 51, 75-77~~ is/are rejected.

☐ Claim(s) ___ is/are objected to.

☐ Claim(s) ___ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on ___ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on ___ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) ___.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: ___.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). ___

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other ___

Office Action Summary

The amendment of 2/11/02 has been entered. The amendment amended the specification and claims 1, 22, 25, 26, 76, 135, 143 and 144.

Claims examined on the merits are 1-26, 51, 75-77, 102, 117-119, 123-125, 135, 136, 143 and 144 which are all claims in the application.

Only one document (Wagner et al) accompanied forms PTO-1449 filed 2/11/02. The other documents are not in the file and have not been found. The documents should be resupplied.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 21, 24, 102, 117-119, 123-125, 135 and 136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Where recited in claims 21, 24, 102, 117-119, 123-125, 135 and 136, "glutamine-rich" and "lysine-rich" are uncertain as to meaning and scope. Being "rich" is relative and subjective.

Applicants assert that the specification defines the terms. However, "rich" in the claims can have a meaning other than as described in the specification. The claims and not the specification define the metes and bounds of the invention, and the claims must be definite without without relying on the specification. If "rich" means "at least 20%", the claims should be amended to require at least 20% of glutamine or lysine instead of reciting "rich".

Claims 1, 3-19, 23, 24, 26, 51, 75-77, 123-125, 135, 136, 143 and 144 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al (5,490,980) in view of Bernstein et al (5,679,377) or

Mathiowitz et al (5,271,961) and each taken with Won (5,145,675) for reasons in the previous office action of 2/11/02.

The claims are drawn to a method of treating a subject by contacting the skin of the subject with microparticles having surface available transglutaminase substrate reactive groups, and in the presence of endogenous or exogenous transglutaminase covalently attaching the microparticles to the skin surface. Also claimed is a kit and composition containing the microparticles.

Richardson et al disclose attaching an active agent inherently containing or modified to contain an alkylamine ($R'NH_2$) group to skin, hair or nails by crosslinking the active agent through the alkylamine group to glutamine residues of skin, hair or nails (col 2, lines 44-68). The active agent may be an intact protein (col 3, line 4).

Bernstein et al disclose protein microspheres that can be made of a prolamine protein containing a high number of hydrophobic amino acids such as glutamine (col 5, lines 26-43). The microspheres can be formed entirely of protein or protein in combination with a polymer. The microspheres can have a size of about 50 to 100 nm to about 20 microns, and preferably from about 100 nm to about 5 microns (paragraph bridging cols 8 and 9). Composite protein-polymer microspheres can be formed by combining the protein with a non-protein natural or synthetic polymer (col 4, line 41 to col 5, line 24). The composite microspheres may be in the form of protein microspheres coated with a polymer or polymer microspheres coated with a protein. The protein can be modified chemically or enzymatically (paragraph bridging cols 6 and 7) to provide a property such as enhanced surface reactivity. Enhanced stability of

the protein may be obtained by crosslinking the protein with transglutaminase (col 7, lines 11-22). The microspheres can be used for delivery of a biologically active agent such as a drug to provide a desired release rate at a targeted site (col 3, lines 40-65). Microspheres containing a desired compound can be topically applied to skin or other areas to provide sustained delivery of the compound (col 10, line 1 to col 11, line 31).

Mathiowitz et al disclose the production and use of protein microspheres essentially as Bernstein et al.

Won et al disclose topically applying porous polymer microspheres containing an active substance to skin to provide controlled release of the active substance for prolonged activity on the skin (col 2, lines 42-50).

It would have been obvious to provide the active agent of Richardson et al in a protein microsphere and use transglutaminase to attach the protein microsphere to skin to provide release of the active agent at a desired rate as suggested by Bernstein et al or Mathiowitz et al and Won using protein or polymer microspheres to deliver an active agent at a desired release rate to a site such as skin. It would have been expected that transglutaminase will crosslink the glutamine of the protein microspheres with glutamine and/or amino groups of skin since it is known to crosslink protein with transglutaminase. When desiring glutamine groups for reacting with transglutaminase, it would have been obvious to omit treating the protein of the microspheres with transglutaminase for crosslinking to increase stability as may be carried out by Bernstein et al or Mathiowitz et al. Forming a kit as in claims 51 and 75-77 would

have been obvious in view of Richardson et al disclosing (col 14, lines 5-12) providing a package containing an active agent and transglutaminase. A composition as required by claims 123-125, 135 and 136 would have been obvious from the references since it would have obvious to provide the protein microspheres with sufficient surface glutamine groups to attach the microspheres to skin with transglutaminase. As to claims 143 and 144, it would have been obvious to use a non-nucleic acid active agent in the protein microsphere when the function of such an agent is desired, and selecting a preferred particle size within the ranges of Bernstein et al or Mathiowitz et al would have required only limited routine experimentation and been obvious. The limitations of dependent claims would have been matters of obvious choice within the ordinary skill of the art in view of the disclosures of the references.

Applicant's arguments filed 2/11/02 have been fully considered but they are not persuasive.

Applicants urge that Richardson et al use exogenous transglutaminase and demonstrates poor binding in the absence of exogenous transglutaminase. However, there is inadequate evidence to establish that using endogenous tansglutaminase in the claimed invention does not result in poorer binding than when using exogenous transglutaminase. One would have expected transglutaminase to be endogenous, and to use only this endogenous source would have been obvious. Moreover, the claims are not limited to using only the endogenous transglutaminase and excluding all exogenous transglutaminase, and endogenous transglutaminase will inherently be present when binding as disclosed by Richardson et al. The

present claims do not require polymers containing lysine or glutamine, and the claims do not exclude the use of an alkyamine as disclosed by Richardson et al.

Applicants urge that there is no evidence that the microspheres of the secondary references have a surface containing a transglutaminase substrate. However, since the microspheres are made of protein they will inherently contain the substrate. There is clear motivation to make the combination since the secondary references teach applying the microspheres to skin for certain uses. Even if the seconday references do not teach attaching the microspheres, the references are combined together and must be considered together as a whole rather than each alone.

Claims 2, 20, 21, 102 and 117-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 1, 3-19, 23, 24, 26, 51, 75-77, 123-125, 135, 136, 143 and 144 above, and further in view of Zheng et al for reasons in the previous action.

The claims require the transglutaminase substrate groups to be lysine.

Zheng et al disclose producing microspheres containing lysine amino groups to covalently link the microspheres to desired molecules. The microspheres are a blend of a poly(lactide-co-glycolide) and poly(ϵ CBZ-L-lysine).

When attaching protein microspheres with transglutaminase to skin as set forth above, it would have been obvious to provide the protein microspheres with lysine groups by blending the protein of the

microspheres with poly(ϵ CBZ-L-lysine) as suggested by Zheng et al since Richardson et al disclose reacting alkylamine groups with transglutaminase to provide attachment of an active agent to skin.

It is granted as urged by applicants that Zheng et al does not teach all elements of the claims. However, the references are used in combination, and all elements become obvious when all the references are considered in combination.

Claims 123-125, 143 and 144 are rejected under 35 U.S.C. 102(b) as being anticipated by Bernstein et al or Mathiowitz et al.

The protein microspheres of Bernstein et al or Mathiowitz et al are inherently glutamine-rich, and inherently contain sufficient transglutaminase reactive substrate groups on their surfaces to attach the microspheres to skin in the presence of endogenous or exogenous transglutaminase as in claims 123-125. Crosslinking protein with transglutaminase as disclosed by Bernstein et al or Mathiowitz et al is optional and not essential. The microspheres of Bernstein et al or Mathiowitz et al can contain a non-nucleic acid active agent and have a particle size in the range of claims 143 and 144.

In response to applicants' argument, as noted above, the microspheres of the references are made of protein and will inherently contain a substrate for transglutaminase.

Claims 1-26, 51, 75-77, 102, 117-119, 123-125, 135, 136, 143 and 144 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-48 of U.S. Patent No. 6,267,957 in view of Berstein et al or Mathiowitz et al and each taken with Won.

The claims of the patent require attaching an agent to body tissue by applying to the body tissue a conjugate of the agent and a linking molecule such as a polymer containing glutamines or lysines in the presence of transglutaminase to crosslink the conjugate to the body tissue via the linking molecule.

For the type of reasons set forth above, it would have been obvious to substitute the conjugate containing an agent in the patent claims with protein microspheres containing the agent as suggested by Berstein et al or Mathiowitz et al and Won.

Claims 22 and 25 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

The fax phone number is (703) 305-3014 or 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DMN
8/9/01

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1651